UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

IMAGE

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

DATE: July 6, 1999

SUBJECT: ID#: 99MS0011. SECTION 18 EXEMPTION FOR THE USE OF FIPRONIL IN/ON **COTTONSEED** IN **MISSISSIPPI.**

DP Barcode:	D255292	Case#:	291825
Submission #:	S560375	Class:	Insecticide
Chemical#:	129121	40 CFR:	180.517
Trade Name:	Regent		

FROM: Susie Chun, Chemist
Marion Copley, D.V.M.
Dana Vogel, Chemist
RAB1/HED (7509C)

THROUGH: George Kramer, Ph.D., Chemist
Melba Morrow, D.V.M., Branch Senior Scientist
RAB1/HED (7509C)

TO: Andrew W. Ertman/Robert Forrest, PM Team 05
MUIERB/RD (7505C)

INTRODUCTION

The Mississippi Department of Agriculture and Commerce has proposed a specific exemption for the use of fipronil on cotton for control of the tarnished plant bug (TPB). This is the first §18 request for this use. The proposed program will entail application of 125,000 pounds of Regent 80WG (100,000 lbs ai) on 500,000 acres statewide from May 15, 1999 until September 1, 1999.

SUMMARY

Tolerances have been established (40 CFR 180.517) for the residues of fipronil, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1*R,S*)-(trifluoromethyl)sulfinyl]-1*H*-pyrazole-3-carbonitrile, and it metabolites 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile, 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile, and 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile, in or on a variety of raw agricultural commodities and processed commodities at levels ranging from 0.02 ppm in corn, field, grain to 0.10 ppm in rice, straw. Meat, milk, poultry

levels ranging from 0.02 ppm in corn, field, grain to 0.10 ppm in rice, straw. Meat, milk, poultry and egg tolerances have been established at levels ranging from 0.01 ppm to 1.50 ppm.

For this Section 18 (S18) petition, fipronil will be applied aerially or by ground equipment to control tarnished plant bug (TPB) on cottonseed. No more than 0.2 lbs ai/Acre will be applied per season. The maximum single application rate is 0.05 lbs ai/Acre. Repeated applications will be made at a 3 to 10 day interval. The pre-harvest interval (PHI) is 45 days.

Aggregate Exposure

The GENEEC EEC for fipronil (+ 3 metabolites) exceeds HED's Drinking Water Level of Comparison (DWLOC). However, GENEEC is a tier 1 estimate and even dividing the EEC by 3 results in a highly conservative estimate. In general, a tier 2 PRZM-EXMs water estimate analysis will result in significantly lower EECs. Therefore, on this basis HED believes that residues of fipronil (+ 3 metabolites) in drinking water (when considered along with other sources of exposure for which HED has reliable data) would not result in levels of chronic aggregate exposure of concern at this time.

HED concludes with reasonable certainty that no harm will result from acute, short-term, or intermediate-term exposure to fipronil (+ 3 metabolite residues). HED bases this determination on a comparison of estimated concentrations of fipronil in surface water and ground water to back-calculated "levels of comparison" for fipronil in drinking water. These drinking water levels of comparison (DWLOC) were determined after HED has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of fipronil (+ MB45950, MB46136, and MB46513) in surface waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of fipronil (+ MB45950, MB46136, and MB46513) on drinking water as a part of the aggregate risk assessment process.

Residential Exposure

MOEs are greater than 1,700 for all handling activities associated with use on pets. MOEs are greater than 5,000 for all post-application exposures associated with use on pets. Therefore, all residential exposures are below HED's level of concern.

Occupational Exposure

The margins of exposure (MOE) are **110** and greater for all occupational handling activities. Therefore, since HED's level of concern for fipronil is for MOEs less than 100, occupational exposure to handlers is below the level of concern. For occupational exposures, the photodegradate is not expected to form during the mixing/loading or application of fipronil. Reentry exposure is also unlikely due to the minimal potential for post-application exposure from the proposed use.

Recommendation for Tolerances

The toxicology, chemistry, and occupational/residential exposure databases are adequate to support the following time-limited tolerances and S18 registration for the use of fipronil in/on cottonseed:

Cotton, undelinted seed	0.5 ppm
Cotton Gin Byproducts	10 ppm
Milk Fat (reflecting 0.4 ppm in milk)	12 ppm
Fat*	3.6 ppm
Meat*	0.5 ppm
Meat byproducts (except liver)*	0.3 ppm
Liver*	1.1 ppm
Hog Fat	0.07 ppm
Eggs	0.06 ppm
Poultry Fat	0.11 ppm
Poultry Meat byproducts	0.04 ppm

*of cattle, goats, horses, sheep

TOXICOLOGICAL ENDPOINTS

The Hazard Identification Assessment Review Committee (HIARC) met on July 10, 1997 to select appropriate endpoints for acute dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) for **fipronil** and on December 9, 1997 to select appropriate endpoints for acute and chronic dietary and short-, intermediate-, and long-term occupational exposure (dermal and inhalation) for the fipronil **photodegradate MB46513**. On January 22, 1998, the HIARC reassessed the potential sensitivity of infants and children and discussed the UFs and/or MOEs for both the parent, **fipronil** and the **photodegradate MB46513**. On April 22, 1998, the HIARC met again to reevaluate the endpoints for fipronil and its photodegradate based on new and reevaluated data. On May 20, 1999, the HIARC met to reexamine and establish endpoints to use for inhalation risk assessment and to revisit the acute reference dose endpoint for **fipronil** (Memo, M. Copley, 6/15/99). The conclusions are presented in the following sections and summarized in Tables 1 and 2.

1. Dietary

a. Acute Toxicity - General Population (including infants and children)

Fipronil

Acute Reference Dose (aRfD) = 0.025 mg/kg/day. The acute RfD is 0.025 mg/kg/day based on the no observed adverse effect level (NOAEL) from the acute neurotoxicity study in the rat (MRID# 44431801) and an uncertainty factor (UF) of 100. The NOAEL of 2.5 mg/kg/day was based on decreased body weight gains, food consumption and feed efficiency in females, and decreased hindlimb splay in males at 7 hours post dosing at 7.5 mg/kg/day (lowest observed adverse effect level (LOAEL)).

$$aRfD = \frac{NOAEL}{UF} = \frac{2.5\ mg/kg/day}{100} = 0.025\ mg/kg/day$$

Since the HED Food Quality Protection Act (FQPA) Safety Factor Committee (SFC[1]) determined to remove the 10x safety factor (SF) (i.e., reduced to 1x), the aRfD is identical to the acute Population Adjusted Dose (aPAD). Therefore the aPAD is 0.025 mg/kg/day for fipronil (parent only).

$$aPAD = \frac{aRfD}{(FQPA\ SF)} = \frac{0.025\ mg/kg/day}{1} = 0.025\ mg/kg/day$$

Photodegradate MB46513 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile]

Acute RfD = 0.02 mg/kg/day. The acute RfD is 0.02 mg/kg/day based on the NOAEL of 2 mg/kg in an acute neurotoxicity study in rats (with the photodegradate, MRID# 44262808) based on significant decreases in locomotor activity in both sexes during the first 30 minutes as well as decreases in hindlimb splay and rectal temperature in both sexes at 6 hours post dosing at 12 mg/kg/day (LOAEL). Since the HED FQPA SFC determined to remove the 10x SF (i.e., reduced to 1x), the acute RfD is identical to the aPAD. Therefore, the aPAD for the photodegradate MB46513 is 0.02 mg/kg/day.

b. Chronic Toxicity

Fipronil

Chronic RfD (cRfD) = 0.0002 mg/kg/day. The HIARC assigned a chronic RfD for fipronil of 0.0002 mg/kg/day using a NOAEL of 0.019 mg/kg/day (0.5 ppm) established from a combined chronic toxicity/ carcinogenicity study in rats and an UF of 100. The LOAEL = 1.5 ppm (M: 0.059 mg/kg/day; F: 0.078 mg/kg/day), based on an increased incidence of clinical signs (seizures and death) and alterations in clinical chemistry (protein) and thyroid parameters (increased TSH, decreased T4).

$$cRfD = \frac{NOAEL}{UF} = \frac{0.019\ mg/kg/day}{100} = 0.0002\ mg/kg/day$$

Since the HED FQPA SFC[2] determined to remove the 10x SF (i.e., reduced to 1x), the chronic RfD is identical to the chronic Population Adjusted Dose (cPAD). Therefore the cPAD is 0.0002 mg/kg/day for fipronil (parent only).

$$cPAD = \frac{cRfD}{(FQPA\ SF)} = \frac{0.0002\ mg/kg/day}{1} = 0.0002\ mg/kg/day$$

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[1]see **FQPA Considerations** section for details

[2]see **FQPA Considerations** section for details

Photodegradate MB46513

Adjusted chronic RfD = 0.00002 mg/kg/day. The adjusted NOAEL is 0.0019 mg/kg/day for the photodegradate MB46513. This adjusted dose was derived by the application of a Potency Adjustment Factor (PAF) of 10 to the chronic NOAEL of 0.019 mg/kg/day for the parent compound (i.e., NOAEL of 0.019 mg/kg/day ÷10 PAF = 0.0019 mg/kg/day). The toxicity profile of the photodegradate MB46513 indicates that this material is *approximately* 10 times more potent than the parent compound when the NOAELs/LOAELs are compared. Thus, the adjusted cRfD is 0.00002 mg/kg/day (adjusted NOAEL (0.0019 mg/kg/day) ÷ UF (100)).

STUDY	Photodegradate MB46513	Fipronil
Acute Oral	LD_{50}= 16 mg/kg	LD_{50} = 92 mg/kg
28-Day Oral - Rat	NOAEL/LOAEL = 0.23 / 2.2 mg/kg/day	NOAEL/LOAEL = 3.4 mg/kg/day (LDT)
90-Day Oral - Mouse	NOAEL/LOAEL = 0.08 / 0.32 mg/kg/day	NOAEL/LOAEL = 1.7 / 3.2 mg/kg/day
90-Day Oral - Rat	NOAEL/LOAEL = 0.029 / 0.18 mg/kg/day	NOAEL =0.33 / 1.9 mg/kg/day
Developmental - Rat	Maternal NOAEL/LOAEL = 1 / 2.5 mg/kg/day Develop. NOAEL/LOAEL = 1 / 2.5 mg/kg/day	Maternal NOAEL/LOAEL = 4 / 20 mg/kg/day Develop. NOAEL/LOAEL= 20 mg/kg/day (HDT)

Since the HED FQPA SFC[3] determined to remove the 10x SF (i.e., reduced to 1x), the chronic RfD for the photodegradate MB46513 is identical to the cPAD. Therefore the cPAD is 0.00002 mg/kg/day for the photodegradate MB46513.

2. Non-Dietary

a. Short- and Intermediate- Term Toxicity (Dermal)

Fipronil

In a 21-day dermal study the **NOAEL = 5 mg/kg/day** based on decreased body weight gain and food consumption in male and female rabbits observed at the LOAEL of 10 mg/kg/day (MRID# 42918644). The dermal NOAEL is supported by the oral NOAEL of 0.05 mg/kg/day established in a developmental neurotoxicity study when used in conjunction with a dermal absorption factor of 1 %. This yields an equivalent dermal dose of 5 mg/kg/day (i.e., 0.05 mg/kg/day ÷ 0.01 dermal absorption factor = 5 mg/kg/day).

Photodegradate MB46513

Adjusted Dose = 0.5 mg/kg/day. This dose was derived from a 21-day dermal study with the parent fipronil (MRID# 42918644) by dividing the actual study NOAEL of 5

[3]see **FQPA Considerations** section for details

mg/kg/day by the PAF of 10 (5÷10 = 0.5 mg/kg/day). The LOAEL was based on decreases in body weight gain and food consumption. The HIARC selected the dose and endpoint from the 21-day dermal study in rabbits with the parent compound.

b. Long-Term (Chronic) Toxicity (Dermal)

Fipronil

HIARC identified a dose and endpoint for long-term dermal exposure. In a combined chronic toxicity/carcinogenicity study (MRID# 42918648) in the rat, the **NOAEL is 0.5 ppm** (M: 0.019 mg/kg/day; F: 0.025 mg/kg/day), based on an increased incidence of clinical signs (seizures and death) and alterations in clinical chemistry (protein) and thyroid parameters (increased TSH, decreased T4) at 1.5 ppm (M: 0.059 mg/kg/day; F: 0.078 mg/kg/day). *NOTE: This study/dose was also used to establish the chronic RfD.* However, the proposed use is not expected to result in long-term exposure. Therefore, no risk assessment is required.

Photodegradate MB46513

Based on the current use pattern for the photodegradate (i.e., 1 application/year at planting), long-term exposure via the dermal route is not expected. Commercial applicators are expected to be exposed during the planting season only. Residential exposures are not chronic in nature as label uses for pets indicate treatment every 1 to 3 months. This risk assessment is **NOT** required.

c. Dermal Penetration

Fipronil

Dermal penetration was determined to be 1% in a dermal penetration study (MRID# 42918635) in rats. For short- and intermediate-term MOE calculations, a dermal toxicity study was used, so a dermal penetration factor for these assessments was not required. However, for long-term MOE calculations, a dermal absorption factor of 1% (<1% in 24 hours) should be used since the NOAEL identified is from an oral study.

Photodegradate MB46513

Dermal penetration was determined to be 2% in a dermal penetration study with the photodegradate (MRID# 44262816) in rats. For short- and intermediate-term MOE calculations, a dermal toxicity study was used, so a dermal penetration factor for these assessments was not required. However, for long term MOE calculations, a dermal absorption factor of 2% (approximately 2% at 10 hours) should be used since the NOAEL identified is from an oral study.

d. Inhalation (Short- and Intermediate- Term Toxicity)

Fipronil

In a developmental neurotoxicity study in the rat, the NOAEL= 0.05 mg/kg/day based on a decrease in group mean pup weights during lactation, and significant increase in time of preputial separation in males at 0.9 mg/kg/day (LOAEL) (MRID# 44039002). Since the NOAEL identified is from an oral study, an absorption factor of 100% should be used in risk calculations. The inhalation exposure component (i.e., µg/lb a.i.), using the 100% absorption rate (default value), application rate, and the number of applications should be converted to an **equivalent oral dose (mg/kg/day)** and compared to the NOAEL of the selected study (0.05 mg/kg/day). **This risk assessment is required**.

Photodegradate MB46513

Inhalation exposure is not expected for the photodegradate. Therefore, an endpoint was not established.

e. Inhalation (Long-Term Toxicity)

Fipronil

In a combined chronic toxicity/carcinogenicity study (MRID# 42918648) in the rat, the **NOAEL is 0.5 ppm** (M: 0.019 mg/kg/day; F: 0.025 mg/kg/day), based on an increased incidence of clinical signs (seizures and death) and alterations in clinical chemistry (protein) and thyroid parameters (increased TSH, decreased T4) at 1.5 ppm (M: 0.059 mg/kg/day; F: 0.078 mg/kg/day). *NOTE: This study/dose was also used to establish the chronic RfD and for the long-term dermal exposure risk assessments.* The inhalation exposure component (i.e., µg/lb a.i.), using the 100% absorption rate (default value), application rate, and the number of applications should be converted to an **equivalent oral dose (mg/kg/day)** and compared to the NOAEL of the selected study (0.019 mg/kg/day).

Photodegradate MB46513

Inhalation exposure is not expected for the photodegradate. Therefore an endpoint was not established.

f. Margin of Exposure (MOE)

The HIARC determined that a MOE of 100 is adequate for occupational exposure risk assessment (Memo, J. Rowland and M. Copley, HED Doc. No. 012607, 5/7/98). A MOE of 100 is also adequate for residential exposure.

g. Aggregate Exposure Risk Assessment

The food and water high end exposures were combined to estimate the acute aggregate risk..

Aggregate oral, dermal, and inhalation exposure risk assessments are **not appropriate** due to differences in the toxicity endpoints observed between the oral (neurotoxicity and alterations in clinical chemistry and thyroid parameters), dermal (decreases in body weight gain and food consumption) and inhalation (developmental effects including, decreases in pup weights during lactation and increases in time of preputial separation) routes.

DETERMINATION OF CANCER RISK

Fipronil has been classified by the HED Cancer Peer Review Committee (document dated July 18, 1997) as a Group C - Possible Human Carcinogen, based on increases in thyroid follicular cell tumors in both sexes of the rat, which were statistically significant by both pair-wise and trend analyses (Oncogenicity Study by Dietary Administration to CD-1 Mice for 78 Weeks. Study # LSR 92/RHA313/0971, MRID# 42918649). There are no cancer studies with the photodegradate MB46513. The RfD methodology should be used to estimate human risk because the thyroid tumors appear to be related to a disruption in the thyroid-pituitary status. There was no apparent concern for mutagenicity (no mutagenic activity).

FQPA CONSIDERATIONS

In assessing the potential for additional sensitivity of infants and children to residues of fipronil, HED considered data from developmental toxicity studies in the rat and rabbit and a 2-generation reproductive toxicity study in the rat. The developmental toxicity studies are designed to evaluate adverse effects on the developing fetus resulting from maternal pesticide exposure during gestation. Reproductive toxicity studies provide information relating to pre- and post-natal effects from exposure to the pesticide, information on the reproductive capability of mating animals, and data on systemic toxicity. The following is based on meetings of the Hazard Identification Assessment Review Committee for fipronil on July 2, 1997, January 29, 1998, and April 22, 1998 and for the photodegradate MB45613 on December 18, 1997, and the FQPA Safety Factor Committee meeting of April 27, 1998.

1. Adequacy of Data

For **fipronil parent**, there are acceptable developmental toxicity studies in rats and rabbits, an acceptable two-generation reproduction study in rats, and an acceptable developmental neurotoxicity study in rats. There are no identified data gaps for the assessment of potential effects on offspring following *in utero* and/or postnatal exposure to fipronil parent. For the **photodegradate MB45613** there is an acceptable developmental toxicity study in rats. No other studies are required for the photodegradate MB45613.

2. Susceptibility Issues:

The toxicology data base is complete. Although there is no evidence of enhanced pre- or post-natal susceptibility in infants and children in the developmental and reproductive toxicity studies, the developmental neurotoxicity study identified a developmental NOAEL which was less than the maternal NOAEL indicating an apparent susceptibility issue. However, the HIARC determined that the evidence was not convincing (*regarding susceptibility*). Valid arguments both for and against the biological relevance of the statistically significant decrease in offspring body weight gain and delayed sexual maturation data (delayed time to preputial separation) observed in this study were considered. The more conservative conclusion regarding the offspring developmental NOAEL and LOAEL for the study was agreed upon by the HIARC, although it was recognized that the offspring effects were marginal and appeared to be at a threshold level; the body weight findings in this study were not supported by results in the reproduction study at similar dose levels; and increased susceptibility to the offspring is not

demonstrated following pre- and/or postnatal dosing in the prenatal developmental toxicity studies or the reproductive toxicity study. The HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence from the fipronil data base when considered as a whole.

a. **Developmental Toxicity Studies** There is no evidence of developmental toxicity in either the rat or rabbit developmental toxicity studies.

i. **Rats**

In an oral developmental toxicity study (MRID# 42977903) in rats with fipronil (parent), the maternal toxicity NOAEL was 4 mg/kg/day. The maternal toxicity LOAEL was 20 mg/kg/day based on reduced body weight gain, increased water consumption, reduced food consumption and reduced food efficiency. The developmental toxicity NOAEL was 20 mg/kg/day (HDT). The developmental toxicity LOAEL was greater than 20 mg/kg/day.

In an oral developmental toxicity study (MRID# 44275001) in rats with the photodegradate MB46513, the maternal toxicity NOAEL was 1.0 mg/kg/day and the LOAEL was 2.5 mg/kg/day, based on an increase in clinical signs of toxicity, reduced body weight gain, food consumption, and food efficiency. The developmental toxicity NOAEL was1.0 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on the slight increase in fetal and litter incidence of reduced ossification of several bones.

ii. **Rabbits**

In an oral developmental toxicity study (MRID# 42918646) in rabbits with fipronil parent, the maternal toxicity LOAEL was equal to or less than 0.1 mg/kg/day based on reduced body weight gain, reduced food consumption and efficiency. The maternal toxicity NOAEL was less than 0.1 mg/kg/day. The developmental toxicity LOAEL was greater than 1.0 mg/kg/day and the developmental toxicity NOAEL was greater or equal to 1.0 mg/kg/day.

b. **Reproductive Toxicity Studies**

Rats. In a two-generation reproductive toxicity study (MRID# 42918647) in rats the LOAEL for parental (systemic) toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females) based on increased weight of the thyroid gland and liver in males and females; decreased weight of the pituitary gland in females; and an increased incidence of follicular epithelial hypertrophy in the females. The NOAEL for parental (systemic) toxicity was 3 ppm (0.25 mg/kg/day for males and 0.27 mg/kg/day for females).

The LOAEL for reproductive toxicity was 300 ppm (26.03 mg/kg/day for males and 28.40 mg/kg/day for females) based on clinical signs of toxicity in the F_1 and F_2 offspring; decreased litter size in the F_1 and F_2 litters; decreased body weights in the F_1 and F_2 litters; decrease in the percentage of F_1 parental animals mating; reduction in fertility index in F_1 parental animals; reduced post-implantation survival and offspring postnatal survivability in the F_2 litters; and delay in physical development in the F_1 and F_2 offspring. The NOAEL for

reproductive toxicity was 30 ppm (2.54 mg/kg/day for males and 2.74 mg/kg/day for females).

c. Developmental Neurotoxicity

In an acceptable developmental neurotoxicity study in rats, the maternal LOAEL was 200 ppm (15 mg/kg/day), based on decreased body weight, body weight gain and food consumption. The maternal NOAEL was 10 ppm (0.90 mg/kg/day). The developmental toxicity LOAEL is 10 ppm (0.90 mg/kg/day), based on a marginal but statistically significant decrease in group mean pup weights during lactation, and a significant increase in time of preputial separation in males. The NOAEL for developmental toxicity was 0.5 ppm (0.05 mg/kg/day). The developmental neurotoxicity LOAEL is 200 ppm (15 mg/kg/day) based on decreased auditory startle response, reduced swimming direction scores, group mean angle measurements and water "Y" maze time trails, and decreased absolute brain weights. The NOAEL for developmental neurotoxicity was 10 ppm (0.90 mg/kg/day).

d. Pre- and Post-Natal Sensitivity

The toxicology data base is complete. Although there is no evidence of enhanced pre or post-natal susceptibility in infants and children in the developmental and reproduction studies, the developmental neurotoxicity study identified a developmental NOAEL which was less than the maternal NOAEL indicating an apparent susceptibility issue. The HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence from the fipronil data base when considered as a whole.

3. Application of the FQPA Safety Factor for this S18

The HIARC recommended that the 10x factor to account for enhanced sensitivity of infants and children (as required by FQPA) should be removed. The HIARC concluded that the apparent increased susceptibility in the developmental neurotoxicity study was not supported by the overall weight-of-the-evidence (including no evidence for increased susceptibility in the developmental and reproductive toxicity studies) from the fipronil data base (Memo, J. Rowland and M. Copley, HED Doc. No. 012607, 5/7/98).

The FQPA SFC met on April 17, 1998. The FQPA SFC recommended that the 10x factor for enhanced sensitivity to infants and children (as required by FQPA) **should be removed** for fipronil and its photodegradate, MB46513 (Memo, B. Tarplee and J. Rowland, HED. Doc. No. 012619, 5/12/98).

Table 1- Toxicological Doses and Endpoints for Fipronil (Parent)

EXPOSURE SCENARIO	Dose (mg/kg/day) and Factors	ENDPOINT AND TOXICOLOGICAL EFFECT	STUDY
Acute (Dietary)	NOAEL = 2.5 UF = 100 FQPA SF = 1	Decreased hind leg splay in males at 7 hours.	Acute neurotoxicity - rat
		Acute RfD = 0.025 mg/kg/day **Acute PAD = 0.025 mg/kg/day**	
Chronic (Dietary)	NOAEL = 0.019 UF = 100 FQPA SF = 1	Increased incidence of seizures and death, alterations in clinical chemistry (protein) and ↑ TSH, ↓ T4.	Chronic/onco rat study
		Chronic RfD = 0.0002 mg/kg/day **Chronic PAD = 0.0002 mg/kg/day**	
Short-Term (Oral)	NOAEL=2.5 MOE=100	Same as Acute (dietary)	Acute neurotoxicity-rat
Short-Term (Dermal)	NOAEL = 5 MOE = 100	Decreased body weight gain and food consumption in ♂s and ♀s in a 21-day dermal study in rabbits. Supported by an oral NOAEL of 0.05 mg/kg/day in a developmental neurotoxicity rat study based in ↓ pup weight during lactation, an ↑ in time to preputial separation in males, and an ↑ in mean motor activity counts for ♀ on Postnatal day 17 when used in conjunction with a 1% dermal absorption factor.	21-day dermal study - rabbit
Intermediate-Term (Dermal)	NOAEL = 5 MOE = 100	Same as Short Term (dermal)	21-day dermal study - rabbit
Long-Term (Dermal)	NOAEL=0.019[1] MOE = 100	Same as Chronic (dietary) Assessment not required with the current use pattern.	Chronic/onco rat study
Short-Term (Inhalation)	NOAEL = 0.05[2] MOE = 100	Decrease in group mean pup weights during lactation, and significant increase in time of preputial separation in males (dietary)	Developmental neurotoxicity - rat
Intermediate-Term (Inhalation)	NOAEL = 0.05[2] MOE = 100	Same as Short-Term (Inhalation)	Developmental neurotoxicity - rat
Long-Term (Inhalation)	NOAEL=0.019[2] MOE = 100	Same as Chronic (dietary); Assessment not required with the current use pattern.	Chronic/onco rat study
Cancer (Dietary/Dermal/ Inhalation)	NA	**Group C - Possible Human Carcinogen** (increases in thyroid follicular cell tumors with fipronil (M&F)). Use chronic RfD to estimate human risk as needed (dermal and inhalation)	

[1] use appropriate dermal absorption factor (1%) since the NOAEL used is from an oral study.
[2] use appropriate inhalation absorption factor (100%) since the NOAEL used is from an oral study.

Table 2. Toxicological Doses and Endpoints for Photodegradate (MB46513)

EXPOSURE SCENARIO	Dose (mg/kg/day) and Factors	ENDPOINT AND TOXICOLOGICAL EFFECT	STUDY
Acute (Dietary)	NOAEL = 2.0 UF = 100 FQPA SF = 1	Decreased locomotor activity as well as decreases in hindlimb splay and rectal temperature	Acute neurotoxicity - rat
	Acute RfD = 0.02 mg/kg/day Acute PAD = 0.02 mg/kg/day		
Chronic (Dietary)	*Adjusted NOAEL = 0.0019 UF = 100 FQPA SF = 1	Increased incidence of seizures and death, alterations in clinical chemistry (protein) and ↑ TSH, ↓ T4.	Chronic/onco rat study (fipronil)
	Chronic RfD = 0.00002 mg/kg/day Chronic PAD= 0.00002 mg/kg/day		
Short- and Intermediate- Term (Dermal)	*Adjusted NOAEL = 0.5	Decreased body weight gain and food consumption in ♂s and ♀s in a 21-day dermal study in rabbits. Supported by a NOAEL of 0.05 mg/kg/day in a developmental neurotoxicity (parent) rat study based in ↓ pup weight during lactation, an ↑ in time to preputial separation in males, and an ↑ in mean motor activity counts for ♀ on Postnatal day 17 when used in conjunction with a 1% dermal absorption factor.	21-day dermal study (fipronil)
Long-Term (Dermal)		Not required. Use pattern (1 appl./year) does not indicate a potential for this exposure; risk assessment not required.	
All time periods (Inhalation)		Not required - Use pattern does not indicate a potential for no inhalation exposure to photodegradate	
Cancer (Dietary/ Dermal/Inhalation)	NA	Group C - Possible Human Carcinogen (increases in thyroid follicular cell tumors with fipronil (M&F)). Use fipronil RfD to estimate human risk as needed (dermal and inhalation).	

* = Adjusted NOAEL obtained by dividing the actual NOAELs established in the studies conducted with the parent compound fipronil and PAF of 10. A PAF of 10 was determined by the Committee based on the toxicity profiles of the **photodegradate MB46513** and **fipronil.**

DIETARY AND RESIDENTIAL EXPOSURES AND RISKS

In examining aggregate exposure, FQPA directs EPA to consider available information concerning exposures from the pesticide residues in food and all other non-occupational exposures. The primary non-food sources of exposure the Agency looks at include drinking water (whether from groundwater or surface water), and exposure through pesticide use in gardens, lawns, or buildings (residential and other outdoor and indoor uses). In evaluating food exposures, EPA takes into account varying consumption patterns of major identifiable subgroups of consumers, including infants and children.

1. From Food and Feed Uses

Tolerances have been established (40 CFR 180.517) for the residues of fipronil, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1*R,S*)-(trifluoromethyl)sulfinyl]-1*H*-pyrazole-3-carbonitrile, and it metabolites 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile, 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile, and 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile, in or on a variety of raw agricultural commodities and processed commodities at levels ranging from 0.02 ppm in corn, field, grain to 0.10 ppm in rice, straw. Meat, milk, poultry and egg tolerances have been established at levels ranging from 0.01 ppm to 1.50 ppm.

Dietary Exposure Evaluation Model (DEEM™) analyses for fipronil (+ metabolites) and its photodegradate (metabolite) MB46513 were performed to provide an estimate of the dietary exposure and associated risk for fipronil (+metabolites) and MB46513 resulting from existing tolerances and proposed tolerances on cotton (Memo, D255832, S. Chun, 6/8/99). The DEEM™ analysis evaluated the individual food consumption as reported by respondents in the USDA 1989-92 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. The dietary exposure analyses are attached (Attachment 1).

Since the HED FQPA SFC determined to remove the 10x FQPA SF (i.e. reduced to 1x), the acute and chronic RfDs are the same value as their respective Population Adjusted Doses (PADs). The PAD is a modification of the aRfD or cRfD to include the FQPA Safety Factor or:

$$PAD = \frac{RfD}{FQPA\ SF}$$

a. Acute Dietary Exposure Analysis

An acute dietary risk assessment is required for fipronil. The HIARC chose a dose and endpoint each for fipronil (including the metabolites MB45950 and MB46136) and for MB46513. The acute reference dose (aRfD) selected for MB46513 was less than the aRfD for fipronil. MB46513 is considered more acutely toxic than the parent. A tier 2 acute dietary analysis has been completed with MB46513's aRfD, incorporating fipronil (and the other 2 metabolites). If further refinements in the acute dietary risk assessment are required in the future, separate acute dietary exposure analyses may have to be performed for MB46513 and fipronil (+2 metabolites) separately. Dietary exposures and associated acute dietary risk are shown in Table 3. HED's level of concern is for dietary exposures >100%

aPAD. Besides the U.S. population, the subgroups included in Table 3 represent all children's subgroups and the highest dietary exposures for their respective subgroups (i.e., females and males).

Table 3 - Acute Dietary Exposure Results (Fipronil, MB45950, MB46136, MB46513)

Subgroups	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.001717	9	0.002911	15	0.004482	22
All infants (<1 year)	0.002869	14	0.004338	22	0.006288	31
Nursing infants (< 1 year)	0.001063	5	0.003089	15	0.003467	17
Non-nursing infants (< 1 year)	0.003223	16	0.004491	22	0.006049	30
Children (1-6 years old)	0.003244	16	0.004382	22	0.005793	29
Children (7-12 years old)	0.002114	11	0.003056	15	0.004438	22
Females (13-19 yrs/np/nn)	0.001309	7	0.002181	11	0.003225	16
Males (13-19 years old)	0.001461	7	0.001985	10	0.002982	15

b. Chronic Dietary Exposure Analysis

The chronic DEEM™ dietary exposure analysis used mean consumption (3-day average). The FQPA SFC removed the 10x SF (i.e., reduced to 1x) resulting in cPADs of 0.0002 mg/kg/day for fipronil (+MB45950 and MB46136) and 0.00002 mg/kg/day for MB46513. HED's level of concern is for chronic dietary exposures greater than 100% cPAD. Chronic dietary exposures for the U.S. population and other subgroups are presented in Tables 4 and 5. HED's level of concern is for dietary exposures >100% cPAD. The other subgroups included represent the highest dietary exposures for their respective subgroups (i.e., infants, children, females, and males).

Table 4 - Chronic Dietary Exposure Results (Fipronil, MB45950, and MB46136)

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.000010	5
Non-nursing Infants	0.000014	7
Children (1 - 6 years old)	0.000027	13
Females (13-19, np/nn)	0.000009	4
Males (13-19 years old)	0.000011	6

Table 5 - Chronic Dietary Exposure Results (MB46513)

Subgroups	Exposure (mg/kg/day)	% cPAD
U.S. Population (48 states)	0.000001	5
Non-nursing Infants	0.000002	8
Children (1 - 6 years old)	0.000003	13
Females (13-19, np/nn)	0.000001	4
Females (13+, nursing)	0.000001	4
Males (13-19 years old)	0.000001	5

The HIARC determined that the metabolite, MB46513 was 10x more toxic than parent fipronil In order to aggregate the dietary risk to fipronil and all 3 metabolites, the dietary exposure to MB46513 can be multiplied by 10 to equate its exposure to fipronil, added to the dietary exposure from fipronil, and compared to the cPAD of fipronil. The total dietary exposures of the U.S. population and children (1-6 years old) are presented in Table 6.

Table 6 - Total Chronic Dietary Exposure (Fipronil, MB45950, MB46136, MB46513)

Subgroup	Dietary Exposure (fipronil, MB45950, & MB46136) mg/kg/day	Dietary Exposure (MB46513 only) mg/kg/day	Converted Dietary Exposure (MB46513 only)[1] mg/kg/day	Total Dietary Exposure mg/kg/day	% cPAD
U.S. Population	0.000010	0.000001	0.000010	0.000020	10
Children (1-6 yrs old)	0.000027	0.000003	0.000030	0.000057	28

[1] Converted Dietary Exposure = Dietary Exposure (MB46513 only) x 10
[2] Total Dietary Exposure = Dietary Exposure (fipronil, MB45950, & MB46136) + Converted Dietary Exposure
[3] % cPAD = [Total Dietary Exposure ÷ cPAD (0.0002 mg/kg/day)] x 100

2. From Drinking Water:

A Drinking Water Level of Comparison (DWLOC) is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses. A DWLOC will vary depending on the toxic endpoint, with drinking water consumption, and body weights. Different populations will have different DWLOCs. HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of monitoring data for pesticides, it is used as a point of comparison against conservative model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. They do have an indirect regulatory impact through aggregate exposure and risk assessments.

HED does not have monitoring data available to perform a quantitative drinking water risk assessment for fipronil (+ 2 metabolites) and MB46513 at this time. EFED provided ground and surface water exposure estimates for the use of fipronil on cotton (Memo, D255291, J. Hetrick, 6/8/99).

a. Surface water

Based on the environmental fate assessment, fipronil and its metabolites (MB46513, MB46136 and MB45950) can potentially move into surface waters. The persistence of parent fipronil ($t_{1/2}$=128 to 300 days) and its transformation products ($t_{1/2}$=700 days) may allow for a substantial fraction of fipronil residues to be available for runoff months after application. Tier 1 GENEEC estimated environmental concentrations(EECs) are summarized in Table 7.

Table 7 - EECs for Fipronil Use on Cotton

GENEEC (µg/L) Parent and Degradate	Peak EEC	56-day EEC	56-day[1] EEC
Parent Fipronil	3.11	1.14	0.380
MB46136	0.255	0.101	0.0337
MB46513	0.880	0.582	0.194
MB45950	0.058	0.029	0.0097
Total (fipronil + MB45950 and MB46136)	3.423	1.27	0.423
Total (fipronil + MB45950, MB46136, and MB46513)	4.303	7.09[2]	2.36

*1 in 10 year EECs are reported.

[1] HED policy allows the 56-day GENEEC value to be divided by 3 to obtain a value for chronic risk assessment calculations. The values in this column have been divided by 3.

[2] In order to aggregate fipronil and all three metabolites for chronic exposure, the GENEEC EEC for MB46513 had to be multiplied by the PAF (10). This results in a 56-day EEC of 5.82 ppb.

The EECs for the individual fipronil degradates are highly dependent on the application rate. Since the individual fipronil transformation products represent only a fraction of the applied fipronil, the application rates of the fipronil degradates are representative of maximum percentage of degradate formation in aerobic soil metabolism studies. EFED notes that MB46513 and MB45950 are not major aerobic soil degradates of fipronil. A major photodegradate of fipronil, MB46513, is expected to be a major degradate for foliar-applied fipronil. The degradate MB45950 appears to be formed in anoxic to suboxic environments. These conditions are not likely to be representative of most surface soils (Memo, D255291, J. Hetrick, 6/8/99).

b. Ground water

The environmental fate data for fipronil indicate a moderate to high persistence and relatively low mobility in terrestrial environments. Based on the SCI-GROW model, acute drinking water concentrations in shallow ground water on highly vulnerable sites are summarized in Table 8.

Table 8 - Acute Groundwater estimates for Fipronil Use on Cotton

SCI-GROW Parent and Degradates	µg/L (ppb)
Parent Fipronil	0.03218
MB46136	0.00154
MB46513	0.01700
MB45950	0.000547
Total (fipronil + MB45950 and MB46136)	0.0343
Total (fipronil + MB45950, MB46136, and MB46513)	0.0513

Chronic concentrations are not expected to be higher than acute values. Highly vulnerable sites are those with low organic matter, coarse textured soils (e.g., sands and loamy sands) and shallow ground water. The fate data for fipronil and its degradates indicate a higher potential mobility on coarse-textured soils (sand or loamy sands). Fipronil and its degradates may pose a threat to ground water contamination within these sensitive areas

(Memo, D255291, J. Hetrick, 6/8/99).

d. Drinking Water Risk

HED's default body weights are: males - 70kg, females - 60kg, and children - 10 kg.

$$DWLOC\ (\mu g/L) = \frac{water\ exposure\ (mg/kg/day)\ x\ (body\ weight)}{consumption\ (L)\ x\ 10^{-3}\ mg/\mu g}$$

Acute

Fipronil (+ MB45950, MB46136, and MB46513)

HED has calculated DWLOCs for acute exposure to fipronil (+MB45950, MB46136, and MB46513) in surface and ground water for the U.S. population and children (1-6 years old) to be **640 ppb and 170 ppb, respectively.**

To calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM™analysis) was subtracted from the aPAD to obtain the acceptable acute exposure to fipronil (+MB45950, MB46136, and MB46513) in drinking water. If new uses are proposed in the future, it may be appropriate to calculate DWLOCs separately for fipronil (+ MB45950 and MB46136) and MB46513.

Chronic

Fipronil (+ MB45950 and MB46136)

HED has calculated DWLOCs for chronic exposure to fipronil (+MB45950 and MB46136) in surface and ground water, the DWLOCs are **6.6** and **1.7 ppb** for the U.S. population and children (1-6 years old), respectively.

To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from the DEEM™ analysis) was subtracted from the cPAD to obtain the acceptable chronic exposure to fipronil (+MB45950 and MB46136) in drinking water.

MB46513

HED has calculated a DWLOC for chronic exposure to MB46513 in surface and ground water, the DWLOCs are **0.67** and **0.17 ppb** for the U.S. population and children (1-6 years old), respectively.

To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from the DEEM™ analysis) was subtracted from the cPAD to obtain the acceptable chronic exposure to MB46513 in drinking water.

Fipronil (+ MB45950, MB46513, MB46136)

In order to aggregate the dietary risk to fipronil and all 3 metabolites, the dietary exposure to MB46513 can be multiplied by 10 to equate its exposure to fipronil and added to the dietary exposure from fipronil. This results in a total dietary exposure of 0.000020 mg/kg/day for the U.S. Population and 0.000057 mg/kg/day for children (1-6 years old).

HED has calculated DWLOCs for chronic exposure to fipronil (+ 3 metabolites). The DWLOCs are **6.3** and **1.4 ppb** for the U.S. population and children (1-6 years old), respectively.

To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from the DEEM™ analysis) was subtracted from the cPAD (of fipronil, 0.0002 mg/kg/day) to obtain the acceptable chronic exposure to fipronil (+ 3 metabolites) in drinking water.

Short- and Intermediate- Term

Fipronil (+ MB45950, MB46513, MB46136)

Since there is post-application, non-food, oral exposure from the registered pet use for children, it is appropriate to aggregate this exposure with dietary and water. The scenario is incidental hand-to-mouth exposure. The short-term NOAEL for non-dietary (oral) exposure is based on the acute dietary dose and endpoint for parent fipronil from the acute neurotoxicity study. The chronic dietary exposure for children (1-6 years old) is 0.000057 mg/kg/day and the short-term non-food oral exposure is 0.000030 mg/kg/day. This results in a total exposure of 0.000087 mg/kg/day and a MOE of 29,000. Therefore, the short-term aggregate risk of the most highly exposed subgroup, children (1-6 years old), is calculated to be a MOE of 44,000 (dietary + residential) (*See Short- and Intermediate- Term Aggregate Exposure Section*).

HED has calculated a DWLOC for short- and intermediate- term exposure to fipronil (+ 3 metabolites). The DWLOC is **250 ppb** for children (1-6 years old).

To calculate the DWLOC for short- and intermediate- term exposure relative to a short-term toxicity dose (in this case the acute dietary dose), the short-/intermediate- term exposure (dietary + residential) was subtracted from the aPAD to obtain the acceptable short-/intermediate- term exposure to fipronil (+ 3 metabolites) in drinking water.

3. From Non-Dietary Uses - Residential Exposure

a. Residential Exposures and Assumptions

HED has identified toxicological endpoints of concern for occupational exposure. The residential exposure is assessed for the Frontline® pet products. Three fipronil products are conditionally registered by Rhône-Merial for flea and tick control, Frontline® Spray Treatment (65331-1), Top Spot™ for Cats (65331-2) and Dogs (65331-3). Fipronil is used to control fleas and ticks on dogs and cats and is applied as a ready-to-use pump spray

(Frontline®) to the fur of the animal or as a ready-to-use, pour-on, spot treatment made along the back of the animal between the shoulder blades (Top-Spot™). Frontline® may be applied by both professional groomers and homeowners. The dosage per pound of the animal's body weight is approximately 5 mg. Repeated applications if necessary may be made once every one to three months during flea or tick season.

Rhône-Merial has submitted exposure studies to support the use of fipronil on dogs and cats for the control of fleas and ticks. There are two studies addressing the application of fipronil: 1) Dermal and Inhalation Exposure of Commercial Pet Groomers During Application of Frontline® Spray Treatment (MRID# 44433302), and 2) Dermal Exposure of Commercial Pet Groomers During the Application of Frontline® Top Spot™. Rhône-Merial has also submitted four studies to address the dislodgeable residues of fipronil from dogs and cats following the application of both the spray treatment and the spot treatment (MRID#s 44433301-09). HED reviewed these studies and assessed the potential residential exposures based on the data that was submitted (Memo, D246176, G. Kramer et. al., 5/22/98). Based on the review of these studies, the dermal and inhalation exposures for residential applicators were estimated to be **3 x 10^{-3}** mg/kg/day and **1.78 x 10^{-6}** mg/kg/day, respectively. The non-dietary, oral (hand-to-mouth) was estimated to be no greater than **3 x 10^{-5}** mg/kg/day. The post-application dermal exposure for toddlers was estimated to be **1 x 10^{-3}** mg/kg/day.

An MOE of 100 is adequate to ensure protection for handler exposures to fipronil via the dermal and inhalation routes. Based on the expected use patterns, only short- and intermediate-term exposures are expected. Therefore, no long-term exposure assessment was performed. Fipronil is classified as a category C, (possible human carcinogen). The HIARC determined that a RfD approach should be used as necessary to assess cancer risks.

b. Residential Exposure Assessment

Table 9 summarizes the exposure estimates for homeowner and toddler exposure to fipronil in Frontline® pet products. These exposure estimates represent exposure to the pet immediately after application of spot or spray treatment. The MOEs and cancer risk were calculated from the exposure estimates obtained from the review of previously submitted studies (Memo, D246176, G. Kramer et. al., 5/22/98). Since more exposure is expected from the Frontline® Spray product, exposure estimates for the Frontline® Spot application are not provided. Exposure to the Frontline® Spray product represents the worst case for all residential scenarios.

In addition, exposure to the photodegradate was not assessed due to minimal potential for exposure to both the residential use products. Residential exposure to the photodegradate is not expected while spraying or handling a recently treated pet as these are brief periods usually occurring indoors. Post-application exposure to the degradate is also not expected due to the products, reportedly strong affinity to the sebum and epidermis of pets.

Table 9 - MOEs for the Use of Fipronil to Control Fleas and Ticks on Dogs and Cats

Receptor	Short-Term Dermal MOE [1]	Intermediate-Term Dermal MOE [1]	Short- and Intermediate-term Inhalation MOE [1]	Non-Dietary Oral MOE [1]
Homeowner spray: application exposure	1,700	1,700	28,000	--
Toddler: post-application exposure	5,000	5,000	--	83,000

[1]MOE = NOAEL/Exposure (dermal NOAEL = 5 mg/kg/day, inhalation = 0.05 mg/kg/day, acute dietary = 2.5 mg/kg/day)

MOEs are 1,700 and greater for all handling activities associated with the use on pets. MOEs are 5,000 and greater for all post-application exposures associated with the use on pets. Therefore, all residential exposures are below HED's level of concern.

DETERMINATION OF SAFETY TO U.S. POPULATION

1. Acute Aggregate Risk

The acute aggregate exposure only includes dietary (food) and water. From the acute dietary (food only) risk assessments, high-end exposure estimates were calculated for the U.S. Population and 26 subgroups. The % aPADs were below HED's level of concern at the 95th percentile for the U.S. population with an acute dietary exposure of 9% aPAD. The highest exposure from the infant and children subgroups is in children (1-6 years old) at 16% aPAD. The results of this analysis indicate that the acute dietary risk associated with the proposed use of fipronil on cottonseed RACs is below HED's level of concern.

The maximum estimated concentrations of fipronil in surface and ground water are less than HED's DWLOCs for fipronil as a contribution to acute aggregate exposure. Therefore, taking into account the uses proposed in this action, HED concludes with reasonable certainty that residues of fipronil (+ MB45950, MB46136, and MB46513) in drinking water (when considered along with other sources of exposure for which HED has reliable data) would not result in unacceptable levels of acute aggregate human health risk at this time. Table 10 summarizes the dietary and water exposure for acute exposure.

Table 10 - Acute Scenario (Fipronil, MB45950, MB46136, and MB46513)

Subgroup	aPAD (mg/kg/day)	NOAEL (mg/kg/day)	Food Exposure (from DEEM™) (mg/kg/day)	Water Exposure (mg/kg/day)	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. Population	0.020	2.0	0.001717	0.01828	0.0513	4.303	640
Children (1-6 years old)	0.020	2.0	0.003244	0.01676	0.0513	4.303	170

2. Chronic Aggregate Risk

Though there are residential uses for fipronil, HED has determined that the registered residential uses of fipronil would not fall under a chronic exposure scenario for the U.S. population, infants, or children. Therefore, chronic aggregate exposure will only include food and water.

For the U.S. population, 10% of the cPAD (is occupied by dietary (food) exposure. The highest infants and children subgroup was children (1-6 years old), with a dietary exposure of 28% cPAD (fipronil + 3 metabolites) .

The estimated average concentrations of fipronil (+ 2 metabolites) in surface and ground water are less than HED's DWLOCs for fipronil (+ 2 metabolites) in drinking water as a contribution to chronic aggregate exposure. The estimated average concentrations of MB46513 in surface and ground water are less than HED's DWLOCs for MB46513.

The GENEEC EEC for fipronil (+ 3 metabolites) exceeds HED's DWLOC. However, GENEEC is a tier 1 estimate and even dividing the EEC by 3 results in a highly conservative estimate. In general, a tier 2 PRZM-EXMs water estimate analysis will result in significantly lower EECs.

Therefore, on this basis HED believes that residues of fipronil (+ 3 metabolites) in drinking water (when considered along with other sources of exposure for which HED has reliable data) would not result in levels of chronic aggregate exposure of concern at this time. Table 10, 11, and 12 summarize the dietary and water exposure.

Table 10 - Chronic Scenario (Fipronil, MB45950, and MB46136)

Subpopulation	Food Exposure (from DEEM™) mg/kg/day	Water Exposure (mg/kg/day)	cPAD mg/kg/day	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. Population	0.000010	0.00019	0.0002	0.0343	0.423	7
Children (1-6 years old)	0.000027	0.000173	0.0002	0.0343	0.423	2

[1] Water Exposure(mg/kg/day) = cPAD (mg/kg/day) - dietary exposure from DEEM™ (mg/kg/day).

Table 11 - Chronic Scenario (MB46513)

Subpopulation	Food Exposure (from DEEM™) mg/kg/day	Water Exposure[1] (mg/kg/day)	cPAD mg/kg/day	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. Population	0.000001	0.00002	0.00002	0.017	0.194	0.7
Children (1-6 years old)	0.000003	0.00002	0.00002	0.017	0.194	0.2

[1] Water Exposure(mg/kg/day) = cPAD (mg/kg/day) - dietary exposure from DEEM™ (mg/kg/day).

Table 12 - Chronic Scenario (Fipronil, MB45950, MB46136, and MB46513)

Subpopulation	Food Exposure (from DEEM™) mg/kg/day	Maximum Water Exposure[1] (mg/kg/day)	cPAD mg/kg/day	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
U.S. Population	0.00002	0.00018	0.0002	0.0513	2.36	6.3
Children (1-6 years old)	0.000057	0.00014	0.0002	0.0513	**2.36**	**1.4**

[1] Water Exposure(mg/kg/day) = cPAD (mg/kg/day) - dietary exposure from DEEM™ (mg/kg/day).

3. Short- and Intermediate-Term Aggregate Risk

Short- and intermediate- term application exposure scenarios exist for adults and children. However, there is no significant post-application exposure to adults. There is post-application exposure to children. For both short- and intermediate-term exposures, aggregate systemic (oral), dermal and inhalation exposure risk assessments are not appropriate due to differences in the toxicity endpoints observed between the oral (neurotoxicity and alterations in clinical chemistry and thyroid parameters), dermal (decreases in body weight gain and food consumption) and inhalation (developmental effects including, decreases in pup weights during lactation and increases in time of preputial separation) routes. Since there is post-application, non-dietary, oral exposure for children, it is appropriate to aggregate this exposure with dietary and water.

The short-term NOAEL for non-dietary (oral) exposure is based on the acute dietary dose and endpoint for parent fipronil from the acute neurotoxicity study. The chronic dietary exposure and calculated dietary MOE is shown below for children (1-6 years old).

Subgroup	Dietary Exposure from DEEM™ [1] (mg/kg/day)	Calculated Dietary MOE[2]
Children (1-6 years old)	0.000057	44,000

[1] Use the total chronic dietary exposure for fipronil (+3 metabolites)
[2] Calculated Dietary MOE = Short-term oral NOAEL ÷ Dietary Exposure

Calculations:

$$Dietary\ MOE = \frac{Short\text{-}term\ NOAEL}{Chronic\ dietary\ exposure}$$

$$= \frac{2.5\ mg/kg/day}{0.000057\ mg/kg/day} = 44{,}000$$

The oral residential exposure is 0.000030 mg/kg/day (MOE=83,000). The calculated dietary MOE for children (1-6 years old) is 9,300.

Subgroup	Calculated Dietary MOE	Non-Dietary Oral MOE (from Table 9) from Residential Use	Total MOE
Children (1-6 years old)	44,000	83,000	29,000

Calculations:

$$Total\ MOE = \frac{1}{\frac{1}{MOE_{food}} + \frac{1}{MOE_{residential}}}$$

$$Total\ short\text{-}term\ MOE = \frac{1}{\frac{1}{44{,}000} + \frac{1}{83{,}000}} = 29{,}000$$

For the short-term aggregate risk of the most highly exposed subgroup, children (1-6 years old), the calculated MOE is 29,000. HED concludes that short- and intermediate- term aggregate MOEs for children are acceptable for the purposes of this S18. The maximum estimated concentrations of fipronil in surface and ground water are less than HED's DWLOCs for fipronil (+ 3 metabolites) as a contribution to short-/intermediate-term aggregate exposure. Therefore, taking into account the uses proposed in this action, HED concludes with reasonable certainty that residues of fipronil (+ MB45950, MB46136, and MB46513) in drinking water (when considered along with other sources of exposure for which HED has reliable data) would not result in short-/intermediate-term aggregate human health risks of concern. Table 13 summarizes the dietary and water short-/intermediate-term exposure.

Table 13 - Short-/Intermediate- Term Scenario (Fipronil, MB45950, MB46136, and MB46513)

Subpopulation	Total Food Exposure (from DEEM™) mg/kg/day	Residential Exposure mg/kg/day	Maximum Water Exposure[1] (mg/kg/day)	aPAD mg/kg/day	SCI-GROW (ppb)	GENEEC (ppb)	DWLOC (ppb)
Children (1-6 years old)	0.000057	0.000030	0.024913	0.025	0.0513	4.303	250

[1] Water Exposure(mg/kg/day) = cPAD (mg/kg/day) - (dietary exposure from DEEM™ (mg/kg/day) + residential exposure (mg/kg/day))

4. Summary

HED concludes that there is a reasonable certainty that no harm will result from acute, short-term, intermediate-term, or chronic aggregate exposure to fipronil (+ 3 metabolite residues). HED bases this determination on a comparison of estimated concentrations of fipronil in surface waters and ground waters to back-calculated "levels of comparison" for fipronil in drinking water. These DWLOCs in drinking water were determined after HED has considered all other non-occupational human exposures for which it has reliable data, including all current uses, and uses considered in this action. The estimates of fipronil (+ MB45950, MB46136, and MB46513) in surface waters are derived from water quality models that use conservative assumptions (health-protective) regarding the pesticide transport from the point of application to surface and

ground water. Because HED considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, DWLOCs may vary as those uses change. If new uses are added in the future, HED will reassess the potential impacts of fipronil (+ MB45950, MB46136, and MB46513) on drinking water as a part of the aggregate risk assessment process.

ENDOCRINE DISRUPTOR EFFECTS

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of this active ingredient and end use products for endocrine disruptor effects.

CUMULATIVE RISK

Fipronil is structurally similar to other members of the pyrazole class of pesticides (i.e., tebufenpyrad, pyrazolynate, benzofenap, etc.). Further, other pesticides may have common toxicity endpoints with fipronil.

EPA does not have, at this time, available data to determine whether fipronil has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. For the purposes of these tolerance actions, therefore, EPA has not assumed that fipronil has a common mechanism of toxicity with other substances.

DETERMINATION OF SAFETY TO OCCUPATIONALLY EXPOSED WORKERS

1. Summary of Use Patterns and Formulations

The state of Mississippi is proposing the use of the active ingredient fipronil on cotton for this S18 request. Regent, (containing **80% fipronil**), is a wettable granular used as a insecticide. For this S18 petition, fipronil will be applied by ground or air to control tarnished plant bug. It will be applied to approximately **500,000 acres** in Mississippi from May 15 through September 1, 1999. No more than 0.2 lbs ai/Acre will be applied per season. The maximum single application rate is 0.05 lbs ai/Acre. Repeated applications will be made at a 3- to 10-day interval with a 45 day pre-harvest interval (PHI). Table 14 summarizes the use pattern of fipronil for the proposed use.

Table 14 - Use Pattern Summary of Fipronil (in Regent) on Cotton

Factors	Quantities
Formulation	wettable granular
Crop to be treated	cotton
Pests	tarnished plant bug
Application methods	ground, air
Maximum application rate	0.05 lb a.i. per acre.

Factors	Quantities
Maximum number of applications	Not specified; Up to 0.2lbs ai/Acre per season
Total Amount of Pesticide to be Used	100,00 lbs ai
Use Period	15 May - 1 September 99
Total Acres to be Treated	500,000
Manufacturer	Rhône-Poulenc

2. Occupational Exposures and Assumptions

An MOE of 100 is adequate to ensure protection for handler exposures to fipronil via the dermal and inhalation routes. Based on use patterns, only short- and intermediate-term exposures are expected. Therefore, no long-term exposure assessment was performed. Fipronil is classified as a category C, (possible human carcinogen). The HIARC determined that a RfD approach should be used as necessary to assess cancer risks.

For occupational exposures, the photodegradate is not expected to form during the mixing/loading or application of fipronil. Reentry exposure is also unlikely due to the minimal potential for post-application exposure from the proposed use.

a. Handler Assumptions and Exposure Assessment

HED has identified toxicological endpoints of concern for occupational exposure.

No chemical specific data is available to assess potential exposure to workers. Therefore, this exposure assessment was done using data available in the Pesticide Handler's Exposure Database (PHED) Surrogate Table (v1.1., 1998). HED's exposure assessment is based on the assumptions in Table 15.

Table 15 summarizes the HED exposure estimates for the mixer/loaders in support of the commercial aerial application of fipronil. This scenario represents the highest exposure of all groups handling fipronil. Since private applicators/handlers cannot treat as large an area in a single day, it is assumed that the commercial applicator will have higher exposure than the private applicator.

Table 15 - Aerial Handler Exposure to Regent C (80% Fipronil)

Job Function	AR (lbs ai/Acre)	Unit Exposure[1] (mg/lb ai)	Aerial Acres/ Day[2]	Average Dermal Daily Dose (ADD)[3] (mg/kg/day)	Average Inhalation Daily Dose (ADD)[3] (mg/kg/day)	Dermal MOE[4]	Inhalation MOE[4]
Aerial mixer/loader	0.05	0.066-D 0.00077-I	840	0.0396	0.0005	130	110

[1] Source: Pesticide Handlers Exposure Database (PHED) V1.1, Surrogate Exposure Table.
[2] Assumptions regarding acreage treated per day from previously submitted use/usage data on cotton (BEAD 11/10/87).
[3] ADD = Unit exposure(µg/lb ai) x AR x Acres/Day x 1/BW (70kg)
[4] MOE = NOAEL/ADD; (where NOAEL = 5 mg/kg/day for dermal and 0.05 mg/kg/day for inhalation)

The MOEs are **110** and greater for all handling activities. Therefore, since HED's level of concern for fipronil is for MOEs less than 100, exposure to handlers is below the level of concern.

b. Worker Post-Application Exposure Assumptions and Assessment

Post-application activities related to cotton consist mainly of mechanical harvesting. Therefore, minimal potential for post-application exposure is expected. Since no potentially significant post-application exposure is expected, this exposure assessment was not performed.

c. Restricted Entry Interval (REI)

Based on fipronil's Tox Category classification of II, the appropriate REI is 24 hours.

d. Incident Reports

There are incident reports through December 1996 (From Memo of Virginia A. Dobozy, 4/1/97; D233461) and from March 17, 1997 to April 13, 1998 (From Memo of Virginia A. Dobozy, 4/29/98; D241621) for companion animals. However, no incidents of human exposure have been reported.

OTHER CONSIDERATIONS

1. Nature of the Residue - Plants

The nature of the residue in cotton was found to be understood for the purposes of an EUP only. The cotton metabolism study was not adequate for the permanent tolerance petition as the application rate (0.67X) was not high enough to allow identification of residues in cottonseed (Memo, D129121, G. Kramer, 11/12/96). This metabolism study will be considered adequate for the purposes of this S18 action only.

The residues of concern are fipronil and its metabolites [*MB46136*] 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile, [*MB45950*] 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile, and [*MB46513*] 5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile (40 CFR 180.517).

2. Nature of the Residue - Animals

The nature of the residue in animals is understood. Fipronil is metabolized by: 1) hydrolysis to the amide (RPA 200766), 2) oxidation to the sulfone MB46136, or 3) reduction to MB45950. HED does not consider metabolite MB46513 to be of concern The HED Metabolism Committee, in a meeting held on 5/28/97, has determined that the fipronil residues of concern for the tolerance expression and dietary risk assessment in animal commodities are the parent and its metabolites MB 46136 and MB 45950 (Memo, D235887, G. Kramer and S. Chun, 12/15/97).

3. Analytical Enforcement Methodology

Plants

An adequate enforcement method (Method EC-95-303, MRID# 43776604) is available for the purposes of this S18 action only. A petition method validation (PMV) was successfully completed with minor revisions recommended by ACL (Memo, D234562, G. Kramer, 4/29/97) . The requirements for analytical enforcement methodology remain unfulfilled for the purposes of the permanent tolerance petition.

Samples are extracted by homogenization in acetonitrile/water (75/25). Solids are removed by filtration and NaCl is added to the extract. After clean-up by liquid/liquid partitioning with hexane, the acetonitrile is removed by rotary evaporation. The aqueous solution is then extracted with dichloromethane. The dichloromethane solution is concentrated and cleaned-up using column chromatography. Fipronil and its metabolites MB45950, MB46136, MB46513, and RPA 200766 are then analyzed using GC with ECD. The LOQ is 0.005 ppm for each analyte in cottonseed .

Animals

A method for the determination of residues of fipronil and its metabolites MB45950 and MB46136 in animal commodities was previously reviewed in conjunction with a petition for corn and animal RACs (Memos, D214376, G. Kramer, 7/25/95 and D222350, G. Kramer, 4/1/96), has undergone a successful PMV (Memo, D220222, G. Kramer, 10/26/95) and a revised method has been submitted. The requirements for analytical enforcement methodology are fulfilled (Memo, D222350, G. Kramer, 4/1/96).

4. Multiresidue Method

A report on Multiresidue testing of fipronil and its metabolites MB45950 and MB46136 (MRID# 43401107) has been received and forwarded to FDA (Memo, G, Kramer 5/9/95). Acceptable recoveries of fipronil and its metabolites were obtained in corn grain using Protocol E. Recoveries in forage were 38-65% using Protocol E. A report on Multiresidue testing of MB46513 (MRID# 44374801) has been received and forwarded to FDA (Memo, S. Chun 12/2/97). Acceptable recoveries of MB46513 were obtained in corn forage using Protocol E and cottonseed using Protocol F. Recoveries were 98.6 ± 9.4% using Protocol E and 89 ± 6.2% using Protocol F.

5. Storage Stability Data

Samples from the submitted field trials and the processing study were stored frozen for a maximum of 14 months prior to analysis. Storage stability data were previously submitted and reviewed in conjunction with a petition for corn and animal RACs (PP#5F04426; D222350, G. Kramer, 4/1/96 and D214376, G. Kramer, 7/25/95). The data demonstrated that residues of fipronil and its metabolites MB45950 and MB46136 are stable under frozen conditions for up to 2 years in/on corn grain, and for 12 months in/on corn forage, fodder, silage, crude oil, refined oil, grain dust, meal, and starch. No storage stability data were submitted for MB46513.

A storage stability study in/on cottonseed and seed processing fractions was submitted (MRID44261804) and a complete review will be done in support of the permanent tolerance. A preliminary review was completed for the purpose of this action only. The data demonstrates that the residues of fipronil and its metabolites MB45950, MB46136, and MB46513 are stable under frozen conditions for up to 12 months in ginned cottonseed, cotton meal, cottonseed hulls, cottonseed crude oil, and cottonseed refined oil. HED will consider that storage stability as been demonstrated for this action.

6. Magnitude of the Residues (Meat, Milk, Poultry, and Eggs)

Secondary residues are expected in animal commodities associated with these S18 uses. Meat/milk/poultry/egg tolerances have been established as a result of other fipronil (+ metabolites) uses. Since the current S18 action results in increased fipronil (+ metabolites) residues in feeding items, it is necessary to recalculate the maximum possible fipronil (+ metabolites) residue levels in animal commodities.

a. Ruminants

An acceptable cow feeding study was submitted in conjunction with PP#5F04426 (Memo, D214376, G. Kramer, 7/25/95).

Tables 16 and 17 present the maximum theoretical dietary burden (MTDB) for beef and dairy cattle, respectively.

Table 16 - MTDB of fipronil for beef cattle using the tolerance level residue levels

RAC	% Diet	% DM	Tolerance Level Residues (ppm)	Contribution to Diet (ppm)
Field Corn Forage	40	40	0.15	0.15
Field Corn Stover	25	83	0.30	0.09
Cotton Gin Trash	20	90	10.0	2.22
Cotton, meal	15	89	0.10	0.017
Totals:	100	-----	----	2.48

$$Contribution\ to\ diet = \frac{Tolerance}{\%DM} \times \%\ in\ diet$$

Table 17 - MTDB of fipronil for dairy cattle using the tolerance level residue levels

RAC	% Diet	% DM	Tolerance Level Residues (ppm)	Contribution to Diet (ppm)
Field Corn Forage	50	40	0.15	0.188
Field Corn Stover	15	83	0.30	0.054
Cotton Gin Trash	20	90	10.0	2.22

Cotton, meal	15	89	0.10	0.017
Totals:	100	------	-----	2.48

$$Contribution\ to\ diet = \frac{Tolerance}{\%DM} \times \%\ in\ diet$$

Based on the estimated maximum dietary burden for beef and dairy cattle of 2.48 ppm, the dietary feeding level from the study are 0.016x, 0.053x, and 0.17x. HED is willing to accept this feeding study for the purposes of this action only. ***Note: The cotton gin trash has increased the dietary burden significantly. A new ruminant feeding study will need to be conducted in support of the permanent petition using 2.48 ppm as the 1x rate.***

Table 18 summarizes the maximum residues in cow tissues from the previously submitted feeding study (Memo, D214376, G. Kramer, 7/25/95). In cases where no residues were detected or <LOQ (0.01 ppm) was reported, a value of ½LOQ (0.005 ppm) will be used in the calculation.

Table 18 - Maximum residues in cow tissues at 0.43 ppm (0.17x) and extrapolated to 1x

Tissue	Fipronil	MB45950	MB46136	Combined	
	Feeding Study (ppm)	Feeding Study (ppm)	Feeding Study (ppm)	Feeding Study (ppm)	Extrapolated (ppm)
Milk	< LOQ	< LOQ	0.052	0.062	0.36
Liver	ND	ND	0.172	0.182	1.05
Kidney	< LOQ	ND	0.035	0.045	0.26
Muscle	< LOQ	ND	0.059	0.069	0.40
Fat	0.051	< LOQ	0.554	0.61	3.52

A comparison of the MTDB value for ruminants to the results of a dairy cow feeding study shows that time-limited tolerances should be established as follows:

Note: The milk tolerance should be expressed in terms of "milkfat" as fipronil is fat soluble. The recommended time-limited tolerance is derived from the estimated maximum residue in whole milk (0.36 ppm) and a theoretical concentration factor of 31x.

Milk Fat (reflecting 0.4 ppm in whole milk) . . . . . 12 ppm
Fat* . . . . . 3.6 ppm
Meat* . . . . . 0.5 ppm
Meat byproducts (except liver)* . . . . . 0.3 ppm
Liver* . . . . . 1.1 ppm

*of cattle, goats, horses, sheep

b. Swine

Tolerances exist for swine commodities. Table 19 presents the maximum theoretical dietary burden (MTDB) for swine.

Table 19 - MTDB of fipronil for swine using the tolerance level residue levels

RAC	% Diet	Tolerance Level Residues (ppm)	Contribution to Diet (ppm)
Field Corn Grain	5	0.02	0.001
Cotton, meal	15	0.1	0.015
Rice Grain	65	0.04	0.026
Rice Bran	15	0.04	0.006
Totals:	100	-----	0.048
Contribution to diet = Tolerance × % in diet			

Based on the estimated maximum dietary burden for beef and dairy cattle of 0.048 ppm, the dietary feeding level from the cow feeding study are 0.8x, 2.7x, and 9.0x.

The existing swine commodity tolerances are adequate with the exception of hog fat. A comparison of the MTDB value for ruminants to the results of a dairy cow feeding study (0.43 ppm) shows that a time-limited tolerance should be established as follows:

Hog Fat ..... 0.07 ppm

c. Poultry

An acceptable poultry feeding study was submitted in conjunction with PP#5F04426 (Memo, D214376, G. Kramer, 7/25/95).

Table 20 presents the MTDB for poultry.

Table 20 - MTDB of fipronil for poultry using the tolerance level residue levels

RAC	% Diet	Tolerance Level Residues (ppm)	Contribution to Diet (ppm)
Cotton, meal	20	0.1	0.02
Rice Grain	60	0.04	0.024
Rice Bran	20	0.04	0.008
Totals:	100	-----	0.052
Contribution to diet = Tolerance × % in diet			

Table 21 summarizes the maximum residues in poultry tissues from the previously submitted feeding study (Memo, D214376, G. Kramer, 7/25/95). In cases where no residues were detected or <LOQ (0.01 ppm) was reported, a value of ½LOQ (0.005 ppm) will be used in the calculation. Based on the estimated maximum dietary burden for beef and dairy cattle of 0.052 ppm, the dietary feeding level from the study are 0.2x, 0.6x, and 2.0x.

Table 21 - Maximum residues in poultry tissues at 0.103 ppm (2.0x) and extrapolated to 1x

Tissue	Fipronil	MB45950	MB46136	Combined	
	Feeding Study (ppm)	Feeding Study (ppm)	Feeding Study (ppm)	Feeding Study (ppm)	Extrapolated (ppm)
Eggs	< LOQ	ND	0.116	0.126	0.06
Liver	< LOQ	ND	0.072	0.082	0.04
Muscle	ND	ND	0.014	0.024	0.01
Skin/Fat	< LOQ	ND	0.214	0.224	0.11

The existing poultry commodity tolerances are adequate with the exceptions of eggs, poultry fat, and poultry meat byproducts. The comparison of the MTDB values for poultry to the results of the poultry feeding study shows that time-limited tolerances should be established as follows:

Eggs ..... 0.06 ppm
Poultry Fat ..... 0.11 ppm
Poultry Meat byproducts ..... 0.04 ppm

7. Magnitude of the Residues - Plants

Ten cotton trials were submitted in support of a cotton EUP (PP# 5G4583) and reviewed (Memo, D219819, G. Kramer, 11/12/96). The levels of MB45950 were below the Limit of Detections (LODs) in all cottonseed samples. The LODs for cottonseed are : 3 ppb for fipronil, MB45950. and MB46513 and 4 ppb for MB46136. The maximum levels of fipronil observed were 0.0044 ppm; of MB46136, were 0.005 ppm; and of MB46513, were 0.0055 ppm. The maximum total residue in any sample was 0.0105 ppm. These field trials were found adequate in support of the EUP.

Fourteen crop field trials have been submitted (MRID# 44261805) and a review will be completed in support of the permanent tolerance petition. A preliminary review was completed for the purpose of this action only. These field trials were conducted in 1995 in AK (2), AZ (1). CA (2), GA (1), LA (1), MS (1), NC (1), OK (1), and TX (4). No analysis was completed for 2 field trials, GA and AK (1) resulting in a total of 12 field trials. The geographic distribution of the field trials is acceptable for this action. Each site comprised of 3 test plots (1 untreated control, 2 treated). One test plot was treated as follows (Treatment 1): An in-furrow application at the time of planting (rate of 0.15 lb ai/A) followed by 2 foliar applications (rate of 0.075 lb ai/A) at 7-10 day intervals (such that the last application was 45 days before harvest). This

results in a total application of 0.30 lb ai/A (1.5 x). One test plot was treated as follows (Treatment 2): 4 foliar applications (rate of 0.075 lb ai/A) at 7-10 day intervals such that the last application was 45 days before harvest resulting in a total application of 0.30 lb ai/A (1.5 x). The cottonseed samples were harvested at 43-46 days after the last application. All samples were stored frozen until ginning. The samples were frozen for maximum of 366 days for cottonseed and 380 days for cotton gin trash. The limit of quantitation (LOQ) for fipronil and each metabolite is 0.01 ppm in cottonseed and 0.100 ppm in gin trash. The LODs for cottonseed are : 0.003 ppm for fipronil, MB45950, and MB46513 and 0.004 ppm for MB46136. The LODs for gin trash are: 0.038 ppm for fipronil, MB46513, and MB45950 and 0.05 ppm for MB46136.

Five cotton field trials were (MRID# 44261806) submitted and a review will be completed in support of the permanent tolerance petition. A preliminary review was completed for the purpose of this action only. These field trials were conducted in 1995 in CA (1), GA (1), LA (1), and TX (2). The test plot was treated with 6 foliar application at a rate of 0.05 lb ai/A at 3-5 day intervals such that the last application was 45 days before harvest. This results in a total application of 0.30 lb ai/A (1.5x). The cottonseed samples were harvested 43-46 days after the last application and stored frozen until analysis. The samples were stored for a maximum of 419 days for cottonseed and 420 days for cotton gin trash.

With this submission of 17 field trials and the 10 prior, the field trial data (27 trials) on cottonseed and 17 field trials on gin trash are adequate for this action. Tables 22 and 23 summarizes the residue levels found in all the field trials.

Table 22 - Cottonseed residue level ranges and averages [1,2]. Total (maximum seasonal) application rate for all treatment types 0.30 lb ai/A (1x)

Treatment	Fipronil (ppm)	MB45950 (ppm)	MB46136 (ppm)	MB46513 (ppm)	Combined Residues[3] (ppm)
EUP Foliar 4@0.075 lbs ai/A (10 field trials)	ND - 0.00935 Avg: 0.00228	All ND Avg: 0.0015	All ND Avg: 0.0015	ND - 0.00465 Avg: 0.00274	ND - 0.00967 Avg: 0.00836
EUP In-furrow @ 0.15 lb ai/A & 2 foliar @0.075 lb ai/A (10 field trials)	ND - 0.00295 Avg: 0.00164	All ND Avg: 0.0015	All ND Avg: 0.0015	ND - 0.00335 Avg: 0.00222	ND - 0.00827 Avg: 0.00715
1995 Foliar 4@0.075 lbs ai/A (12 field trials)	ND - 0.00325 Avg: 0.00248	All ND Avg: 0.0015	ND - 0.00325 Avg: 0.00208	ND - 0.0185 Avg: 0.00592	ND - 0.0340 Avg: 0.0127
1995 In-furrow @ 0.15 lb ai/A & 2 foliar @0.075 lb ai/A (12 field trials)	ND - 0.00325 Avg: 0.00208	All ND Avg: 0.0015	All ND Avg: 0.0015	ND - 0.0355 Avg: 0.00558	ND - 0.0460 Avg: 0.0114
1995 Foliar 6@0.05lbs ai/A (5 field trials)	ND - 0.01 Avg: 0.0063	All ND Avg: 0.0015	All < LOQ Avg: 0.005	ND - 0.02 Avg: 0.0085	ND - 0.0388 Avg: 0.0222
Total Avg (in-furrow)	0.00188	0.0015	0.0015	0.00406	0.00944

Table 22 - Cottonseed residue level ranges and averages [1, 2]. Total (maximum seasonal) application rate for all treatment types 0.30 lb ai/A (1x)

Treatment	Fipronil (ppm)	MB45950 (ppm)	MB46136 (ppm)	MB46513 (ppm)	Combined Residues[3] (ppm)
Total Avg (foliar only)	0.00311	0.0015	0.00241	0.00522	0.0128
Total Avg All (27 field trials)	0.00256	0.0015	0.002	0.00470	0.0113

[1] Non-detects (ND) (<LOD) were calculated as ½LOD (0.0015 ppm for fipronil, MB45950, MB46136 and 0.002 ppm for MB46513); <LOQ were calculated as ½LOQ (0.01 ppm for fipronil and each metabolite)
[2] Residue values are the of averages of replicate samples. (i.e. Each test plot had two samples. If the residue values from a sample were 0.0038 and 0.0055 ppm, then an average of these two values was used, 0.0046 ppm)
[3] Combined Residues = (Fipronil x 1.00) + (MB45950 x 1.04) + (MB46136 x 0.97) + (MB46513 x 1.12)

Table 23 - Cotton Gin Trash residue level ranges and averages [1, 2]. Total (maximum seasonal) application rate for all treatment types 0.30 lb ai/A (1x)

Treatment	Fipronil (ppm)	MB45950 (ppm)	MB46136 (ppm)	MB46513 (ppm)	Combined Residues[3] (ppm)
1995 Foliar 4@0.075 lbs ai/A (12 field trials)	ND - 1.497 Avg: 0.233	ND - 0.2385 Avg: 0.0462	ND - 0.986 Avg: 0.330	ND - 4.565 Avg: 0.936	ND - 7.814 Avg: 1.650
1995 In-furrow @ 0.15 lb ai/A & 2 foliar @0.075 lb ai/A (12 field trials)	ND - 0.594 Avg: 0.141	All ND Avg: 0.019	ND - 0.416 Avg: 0.187	ND - 1.8625 Avg: 0.533	ND - 3.045 Avg: 0.940
1995 Foliar 6@0.05lbs ai/A (5 field trials)	ND - 1.6245 Avg: 0.435	ND - 0.247 Avg: 0.0832	0.111 - 1.182 Avg: 0.537	0.176 - 4.742 Avg: 1.391	ND - 8.338 Avg: 2.600
Total Avg (foliar only)	0.292	0.0571	0.391	1.070	1.930
Total Avg All (17 field trials)	0.230	0.0413	0.307	0.848	1.520

[1] Non-detects (ND) (<LOD) were calculated as ½LOD (0.019 ppm for fipronil, MB45950, MB46136 and 0.025 ppm for MB46513); <LOQ were calculated as ½LOQ (0.05 ppm for fipronil and each metabolite)
[2] Residue values are the of averages of replicate samples. (i.e. Each test plot had two samples. If the residue values from a sample were 0.0038 and 0.0055 ppm, then an average of these two values was used, 0.0046 ppm)
[3] Combined Residues = (Fipronil x 1.00) + (MB45950 x 1.04) + (MB46136 x 0.97) + (MB46513 x 1.12)

The results at 1X show a range of residues in cottonseed of <LOD-0.00825 ppm for fipronil, <LOD for MB45950, <LOD-0.005 ppm for MB46136, <LOD-0.0185 ppm for MB46513, and <LOD- 0.460 ppm for combined residues (fipronil + 3 metabolites). The results at 1X show a range of residues in cotton gin trash of <LOD-1.624 ppm for fipronil, <LOD-0.247 ppm for MB45950, <LOD-1.182 ppm for MB46136, <LOD-4.742 ppm for MB46513, and <LOD- 8.338 ppm for combined residues (fipronil + 3 metabolites). **Time-limited tolerances for the combined residues of fipronil and its 3 metabolites should be established at 0.5 ppm for cotton, undelinted seed and 10.0 ppm for cotton gin byproducts.**

8. Processed Food/Feed

A cottonseed processing study (MRID# 43776607) was reviewed in conjunction with the EUP (PP# 3G04583: Memo, D219819, G. Kramer, 11/12/96). Residues of fipronil and its metabolites do not appear to concentrate in cotton processed commodities. Tolerances for residues of fipronil and its metabolites on cotton processed fractions will not be required.

9. Rotational Crop Restrictions

No confined or field rotational crop studies were submitted with this petition. An acceptable confined rotational crop study with radishes, lettuce, grain sorghum, and wheat was submitted and reviewed in conjunction with PP#5F04426 (Memos, D222350, G. Kramer, 4/1/96; D228385, G. Kramer, 8/26/96; and D235683, G. Kramer, 8/11/97). Data from the confined rotational crop study support plantback intervals of 1 month for leafy vegetables, 5 months for root crops, and 12 months for small grains and all other crops. The petitioner has reported that limited rotational crop field trials are in progress. The label submitted with this S18 contains the appropriate plantback intervals.

10. Anticipated Residues

A preliminary dietary exposure was performed with tolerance level residues and 100% crop treated (CT) and the dietary risk was found to exceed HED's level of concern. In order to further refine the dietary risk, anticipated residues (ARs) have been calculated and shown in Tables 23 (acute), 24 (chronic) and 25 (chronic-MB46513). ARs were calculated and incorporated in support of a tolerance on rice (PP#7F4832, Memo, D235887, G. Kramer and S. Chun, 12/15/97). With the proposed use on cottonseed RACs, those ARs need to be revised. Since the current S18 action results in increased fipronil (+metabolites) residues in animal feeding items, it is necessary to recalculate the ARs for animal commodities (Memo, D255833, S. Chun, 5/19/99).

The revised ARs (incorporating cottonseed RACs) will be applicable in support of this S18 action only.

Tables 24-26 present the ARs to be used in the dietary exposure Memo, D255833, S. Chun, 5/19/99).

Acute

Table 24 - Summary of Fipronil + MB46136 + MB45950 + MB46513 Residues for Acute Dietary Risk Assessment

Commodity	AR to Use in Acute Dietary Exposure Analysis (ppm)
Corn Grain[1, 6] **Includes processed commodities**	0.015
Rice Grain[4, 6] **Includes processed commodities** **Excludes wild rice**	0.021
Cottonseed[5, 6] **Includes processed commodities**	0.011
Meat[3]	0.089

Commodity	AR to Use in Acute Dietary Exposure Analysis (ppm)
Liver[3]	0.23
Meat byproducts (except liver)[3]	0.058
Fat[3]	0.78
Milk Fat[2]	1.02
Hog Meat	0.0021
Hog Liver	0.0056
Hog Meat byproducts (except liver)	0.0014
Hog Fat	0.019
Poultry meat	0.0031
Poultry meat byproducts	0.011
Poultry fat	0.029
Eggs	0.016

1 Since residues do not concentrate in processed commodities of corn, the anticipated residue of 0.015 ppm should be used for such commodities in the dietary exposure analysis (i.e. corn oil, meal, etc.).

2 All residues in milk are assumed to concentrate in fat, a value of 0 ppm should be used for other milk fractions

3 These anticipated residues should also be used for meat, fat and meat byproducts of horses, goats and sheep in the dietary exposure analysis.

4 Since residues do not concentrate in processed commodities of rice, the anticipated residue of 0.021 ppm should be used for such commodities in the dietary exposure analysis (i.e. flour, etc.).

5 Since residues do not concentrate in processed commodities, the AR of 0.011 should be used for such commodities in the dietary exposure analysis (i.e., cotton meal, cottonseed oil).

6 Blended commodities will use the average field trial value.

Note: MB46513 is considered more acutely toxic than the parent. A dietary analysis will be done with its dose and endpoint, incorporating fipronil (+2 metabolites). If further refinements in the acute dietary risk assessment are required in the future, a separate dietary exposure analysis will be performed MB46513 and fipronil (+2 metabolites) separately.

Chronic

Table 25 - Summary of Fipronil + MB46136 + MB45950 ARs for Chronic Dietary Risk Assessment

Commodity	% CT or %Anticipated Market Share	AR to use in Chronic Dietary Exposure Analysis[6] (ppm)
Corn Grain[1] **Includes processed commodities**	7	0.015
Rice Grain[4] **Includes processed commodities Excludes wild rice**	11	0.015
Cottonseed[5]	3.6	0.006
Meat[3]	-----	0.00074
Liver[3]	-----	0.0019
Meat byproducts (except liver)[3]	-----	0.00048
Fat[3]	-----	0.0065
Milk Fat[2]	-----	0.017

Commodity	% CT or %Anticipated Market Share	AR to use in Chronic Dietary Exposure Analysis[6] (ppm)
Hog Meat	-----	0.00014
Hog Liver	-----	0.00036
Hog Meat byproducts (except liver)	-----	0.000089
Hog Fat	-----	0.0012
Poultry meat	-----	0.00021
Poultry meat byproducts	-----	0.00071
Poultry fat	-----	0.0019
Eggs	-----	0.0011

1 Since residues do not concentrate in processed commodities of corn, the anticipated residue of 0.001 ppm should be used for such commodities in the DEEM™ analysis (i.e. corn oil, meal, etc.) except corn sugar for which processing data are not available.

2 All residues in milk are assumed to concentrate in fat, a value of 0 ppm should be used for other milk fractions

3 These anticipated residues should also be used for meat, fat and meat byproducts of horses, goats and sheep in the DEEM™ analysis.

4 Since residues do not concentrate in processed commodities of rice, the anticipated residue of 0.015 ppm should be used for such commodities in the DEEM™ analysis (i.e. flour, etc.).

5 Since residues do not concentrate in processed commodities of cottonseed, the anticipated residue of 0.0016 ppm should be used for such commodities in the DEEM™ analysis (i.e. cotton meal, cottonseed oil, etc.).

6 The ARs in the RACs **do not** incorporate %CT or % Anticipated Market Share.

Table 26 - Summary of MB46513 ARs for Chronic Dietary Risk Assessment

Commodity	% CT or %Anticipated Market Share	AR to use in Chronic Dietary Exposure Analysis[6] (ppm)
Corn Grain[5] **Includes processed commodities**	7	0
Rice Grain[3] **Includes processed commodities Excludes wild rice**	11	0.005
Cottonseed[4]	3.6	0.0047
Meat[2]	-----	0.000069
Liver[2]	-----	0.00018
Meat byproducts (except liver)[3]	-----	0.000045
Fat[2]	-----	0.00061
Milk Fat[1]	-----	0.0019
Hog Meat	-----	0.0000085
Hog Liver	-----	0.000022
Hog Meat byproducts (except liver)	-----	0.0000055
Hog Fat	-----	0.000075
Poultry meat	-----	0.000010
Poultry meat byproducts	-----	0.000035
Poultry fat	-----	0.000097
Eggs	-----	0.000054

1 All residues in milk are assumed to concentrate in fat, a value of 0 ppm should be used for other milk fractions

2 These anticipated residues should also be used for meat, fat and meat byproducts of horses,

goats and sheep in the DEEM™ analysis.

[3] Since residues do not concentrate in processed commodities of rice, the anticipated residue of 0.005 ppm should be used for such commodities in the DEEM™ analysis (i.e. flour, etc.).

[4] Since residues do not concentrate in processed commodities of cottonseed, the anticipated residue of 0.0016 ppm should be used for such commodities in the DEEM™ analysis (i.e. cotton meal, cottonseed oil, etc.).

[5] MB46513 is not a metabolite found in corn. Therefore, an AR of 0 ppm can be used for corn RACs.

[6] The ARs in the RACs **do not** incorporate %CT or % Anticipated Market Share.

11. International Residue Limits

There are no Codex, Canadian, or Mexican maximum residue limits (MRLs) established for fipronil and its metabolites on the commodities included in this S18 request. Thus, harmonization is not an issue for this S18 action.

SUPPLEMENTAL INFORMATION

Dietary Exposure

Table 27 - Residue Consideration Summary Table

PARAMETER	PROPOSED USE	RESIDUE DATA
CHEMICAL	Fipronil	Fipronil
FORMULATION	REGENT® 80 WG Insecticide (Rhône-Poulenc Ag Company, EPA Reg. No. 264-XXX)	EXP 60720A Insecticide is a water dispersible granular formulation containing 80% by weight
CROP	Cottonseed	Cottonseed
TYPE APPLICATION	Ground, Air	Ground, Air
# APPLICATIONS	Not specified	1) In-furrow application and 2 foliar applications (7-10 day intervals) 2) 4 foliar applications (7-10 day intervals) 3) 6 foliar applications (3-5 day intervals)
TIMING	3 to 10 day intervals	3- to 10-day intervals
RATE/APPLICATION	0.75 - 1.0 ounces product/A 0.0375-0.05 lbs ai/A	in-furrow - 0.15 lb ai/A, 2 foliar (0.075 lb ai/A each) 4 foliar - 0.075 lb ai/A each 6 foliar - 0.05 lb ai/A each
RATE/YEAR or SEASON	4 ounces product/A/crop 0.2 lbs ai/A/crop	0.30 lbs ai/A/crop
MAXIMUM RESIDUE	N/A	Cottonseed: 0.038 ppm (6 apps @ 0.05 lbs ai/A) Cotton Gin Trash: 8.34 ppm (6 apps @ 0.05 lbs ai/A)
RESTRICTIONS	45-day PHI 12-month plantback interval for small grains or other rotational crops 5-month plantback interval for root crops	45-day PHI 12-month plantback interval for small grains or other rotational crops 5-month plantback interval for root crops 1-month plantback interval for leafy crops
RESIDUE DATA SOURCE	N/A	Rhône-Poulenc
PERFORMING LAB	N/A	Rhône-Poulenc

Additional Information

Progress Toward Registration.

This is the first S18 request for the use of fipronil on cottonseed RACs. A petition (PP# 7F4832) has been submitted by the petitioner for a permanent tolerance on cottonseed RACs.

Reregistration Status.

Fipronil is not a FIFRA '88 reregistration active ingredient.

Attachment1: Dietary Analyses (S. Chun, 6/2/99)
Attachment2: CODEX Form

cc with Attachments: S. Chun (RAB1), M. Copley (RAB1), D. Vogel (RAB1), Ann Sibold (RD)
RDI: M. Morrow (7/1/99), Team (6/15/99), RAB1 Chemists (6/17/99), RAB1 (6/23/99)
S. Chun:811-Bay:CM#2:(703)305-2249:7509C:RAB1

Attachment 1: Dietary Analysis (Available electronically)

Attachment 2: Codex Form

INTERNATIONAL RESIDUE LIMIT STATUS

Chemical Name:	Common Name:	☒ Proposed tolerance ☐ Reevaluated tolerance ☒ Other: Existing tolerances	Date:
5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1*R,S*)-(trifluoromethyl)sulfinyl]-1*H*-pyrazole-3-carbonitrile	Fipronil		5/12/99
5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile	MB45950		
5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl]-1H-pyrazole-3-carbonitrile	MB46136		
5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile	MB46513		

Codex Status (Maximum Residue Limits)	U. S. Tolerances
X No Codex proposal step 6 or above ☐ No Codex proposal step 6 or above for the crops requested Fipronil is scheduled for introduction as a new chemical in 2000.	Petition Number: 98MS0011 DP Barcode: D255292 Other Identifier:
Residue definition (step 8/CXL):	Reviewer/Branch: Susie Chun/ RAB1
	Residue definition: expressed as fipronil [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(1R,S)-(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile] and its metabolites MB45950 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)thio]-1H-pyrazole-3-carbonitrile]; MB46136 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-4-[(trifluoromethyl)sulfonyl[-1H-pyrazole-3-carbonitrile]; and MB46513 [5-amino-1-(2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(1R,S)-(trifluoromethyl)]-1H-pyrazole-3-carbonitrile]

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Corn, field, grain	0.02
		Corn, field, stover	0.30
		Corn, field, forage	0.15
		Rice, grain	0.04
		Rice, straw	0.10
		Eggs	0.06
		Fat*	3.6
		Meat byproducts (except liver)*	0.5

Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Meat*	0.3
		Liver*	1.1
		Hog Fat	0.07
		Hog Liver	0.02
		Hog Meat	0.01
		Hog Meat byproducts (except liver)	0.01
		Milk, fat (reflecting 0.4 ppm in whole milk)	12.0
		Poultry Fat	0.11
		Poultry Meat	0.02
		Poultry Meat byproducts	0.04
		Cottonseed	0.5
		Cotton Gin Trash	10.0

Limits for Canada	Limits for Mexico
X No Limits □ No Limits for the crops requested	□ No Limits □ No Limits for the crops requested
Residue definition: N/A	Residue definition: Fipronil

Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
		maize	0.01

Notes/Special Instructions:

13544

002342

Chemical:	**Fipronil**
PC Code:	**129121**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**07/06/99**
File ID:	**DPD255292**
Accession Number:	**412-01-0084**

HED Records Reference Center
01/19/2001